Reconocimiento de trastorno de flujo linfático neonatal: Resultados de RM fetal y RM postnatal. Correlación con Linfangiogramas.

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Justificación y objetivos: este estudio tuvo como objetivo describir las características de la imagen prenatal y postnatal en los resultados de los recién nacidos con trastornos linfáticos (LND).
Materiales y métodos: Una búsqueda aprobada por la junta de revisión institucional de la base de datos de radiología para pacientes con LND identificó cinco pacientes. Los criterios de inclusión consideran imágenes prenatales (resonancia magnética fetal [RM], ultrasonido) y tridimensionales postnatales con Sistema de Muestreo perfeccionado T2, de aplicación de contrastes optimizados que utilizan diferentes ángulos de giro (SPACE) evolutivos y dinámicos.
Además una Linfangiografía por RM a los 6 meses de vida. Se realizó una revisión gráfica para evaluar la morbilidad y la mortalidad.
Resultados: Se identificó el hallazgo prenatal de "pulmón de la nuez moscada" o trastorno linfático pulmonar fetal en los cinco pacientes con RM fetal y en cuatro de cinco pacientes por ultrasonido fetal. La linfangiografía de RM postnatal con contraste dinámico demostró Flujo linfático pulmonar anormal en cuatro de cinco pacientes, pero ausente en un solo paciente con síndrome del corazón izquierdo hipoplásico coexistente (HLHS).
Se observó reflujo dérmico en un paciente, también el único paciente con edema prenatal de la pared del cuerpo. Tres pacientes con flujo linfático pulmonar se clasificaron como quilotórax neonatal. El paciente con reflujo dérmico y perfusión pulmonar fue diagnosticado con trastorno del flujo linfático central (CLFD). El paciente con HLHS con perfusión linfática normal mantuvo el diagnóstico de HLHS. De cinco pacientes, el paciente con CLFD y el que tenía HLHS expiraron debido a una dificultad respiratoria.
Conclusiones: los NLD se pueden reconocer en imágenes prenatales y postnatales y pueden ser primarios, como en el quilotórax neonatal o CLFD,
o secundaria. En esta pequeña serie, el "pulmón de la nuez moscada" estuvo presente en todos los pacientes. Las imágenes prenatales demuestran que el edema de la pared corporal puede se correlacionan con el reflujo dérmico postnatal, que, en nuestra pequeña cohorte, tuvo un mal pronóstico.

Original Investigation

Recognition of Neonatal Lymphatic Flow Disorder: Fetal MR Findings and Postnatal MR Lymphangiogram Correlation

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Rationale and Objectives: This study aimed to describe prenatal and postnatal imaging features and outcomes of neonates with neonatal lymphatic disorders (NLDs).

Materials and Methods: An institutional review board-approved search of the radiology database for patients with NLD identified five patients. Inclusion criteria include prenatal imaging (fetal magnetic resonance [MR] imaging and ultrasound) and postnatal three-dimensional T2 Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) and dynamic contrast-enhanced MR lymphangiography within 6 months of life. Chart review was undertaken to evaluate morbidity and mortality.

Results: Prenatal finding of "nutmeg lung" or fetal pulmonary lymphatic disorder was identified in all five patients on fetal MR imaging, and in four of five patients on fetal ultrasound. Postnatal dynamic contrast-enhanced MR lymphangiography demonstrated abnormal lymphatic flow to the lungs in four of five patients, but absent in the single patient with coexisting hypoplastic left heart syndrome (HLHS). Dermal backflow was seen in one patient, also the only patient with prenatal body wall edema. Three patients with lymphatic flow to the lungs only were classified as neonatal chylothorax. The patient with dermal backflow and perfusion to the lungs was diagnosed with central lymphatic flow disorder (CLFD). The HLHS patient with normal lymphatic perfusion maintained the HLHS diagnosis. Of the five patients, the patient with CLFD and the one with HLHS expired because of respiratory distress.

Conclusions: NLDs can be recognized on prenatal and postnatal imaging and may be primary, as in neonatal chylothorax or CLFD, or secondary. In this small series, "nutmeg lung" was present in all patients. Prenatal imaging demonstrates that body wall edema may correlate with postnatal dermal backflow, which, in our small cohort, carried a poor prognosis.

Key Words: Neonatal lymphatic disorders; MR imaging; fetal imaging.

INTRODUCTION

Neonatal lymphatic disorders (NLD) are a group of rare diseases that clinically manifest as one or a combination of chylous pleural effusion, chylous ascites, and soft tissue edema. Various terms are found in the literature to describe these conditions, including congenital chylothorax (1), non–immune neonatal hydrops fetalis, congenital lymphatic dysplasia (2), congenital pulmonary lymphangiectasia (3), and primary lymphatic dysplasia (4).

These disease processes are difficult to evaluate in part because of the rarity of these conditions and the lack of an effective minimally invasive lymphatic imaging method. Bellini et al. used lymphoscintigraphy to identify the lymphatic flow patterns in patients with NLD and demonstrated several findings, including congenital aplasia or hypoplasia of the peripheral lymphatics, congenital abnormalities of the abdominal or thoracic lymphatic trunks, and congenital lymphatic valvular incompetence (5). One of the advantages of lymphoscintigraphy is the ability to demonstrate the dynamics of lymphatic flow; however, its spatial resolution is significantly limited. Dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL) is a new lymphatic imaging technique that allows imaging of the central lymphatic system through the delivery of a gadolinium-based contrast agent into the inguinal lymph nodes under ultrasound (US) guidance (6,7). DCMRL provides both dynamic flow and anatomic information. Using this technique, Dori et al. and Itkin et al. visualized abnormal pulmonary lymphatic flow from the thoracic duct toward lung parenchyma in adult and pediatric patients with plastic

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bronchitis, a finding they named pulmonary lymphatic perfusion syndrome (7–9).

Over the last decade, fetal magnetic resonance imaging (MRI) has become an important tool in diagnosis of prenatal disorders (10,11). Recently, the appearance of pulmonary lymphangiectasia on fetal MRI has been described by the term "nutmeg lung," which pertains to findings of heterogeneous lung signal with thin T2 hyperintense branching tubular structures extending from the hilum to the lung periphery (12). Findings of "nutmeg lung" are often accompanied by pre- or postnatal pleural effusion and have been seen in association with hypoplastic left heart syndrome (HLHS) (12–14).

Correlation of prenatal imaging findings of these disorders with postnatal lymphatic imaging has not been established. The purpose of this study is to describe prenatal and postnatal imaging features and outcomes of neonates with NLD.

MATERIALS AND METHODS

After institutional review board approval, a retrospective review was performed on all patients diagnosed with NLD who underwent DCMRL and prenatal imaging at our institution between January 1, 2013, and August 1, 2016. The patients who had prenatal imaging consisting of both fetal US and MRI and postnatal imaging within 6 months of life consisting of a three dimensional (3D) T2 Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) and DCMRL were included in the study. DCMRL was performed as previously described using XMR suite that combines an MR scanner and catheterization laboratory (Siemens, Erlangen, Germany) (7). Briefly, bilateral inguinal lymph nodes were accessed with 25G needles using US guidance, and the position was confirmed with injection of the iodinated contrast under fluoroscopy. The patient was then transferred to the MR scanner, and slow injection of gadobutrol (Gadavist, Bayer HealthCare, Whippany, NJ) at 0.5–1.0 mL/min was performed. Time-resolved MR angiography was then performed beginning 1 minute after injection at intervals of 20–30 seconds, for a total of 15 minutes. Finally, a navigated 3D spoiled gradient echo sequence was performed.

The prenatal MR studies were reviewed by two pediatric radiologists in consensus for the presence or absence of "nutmeg lung," pleural effusion, pericardial effusion, ascites, and body wall edema. The prenatal US examinations were reviewed by a single pediatric radiologist specializing in maternal-fetal imaging for the presence or absence of "nutmeg lung," pleural effusion, pericardial effusion, ascites, and body wall edema. "Nutmeg lung" was defined as the heterogeneous appearance of the lung parenchyma with tubular T2 intense throughout the parenchyma, thought to represent dilated lymphatics (12,13).

Two pediatric radiologists and an interventional radiologist specializing in lymphatic imaging and interventions reviewed the postnatal 3D T2 SPACE and DCMRL studies in consensus. The 3D T2 SPACE was evaluated for the presence or absence of increased signal in the soft tissues of the upper chest and neck, axilla, perihilar region, lungs in an interstitial distribution, periportal region, mesentery, body wall, and upper thigh. In addition, the presence or absence of ascites and pleural and pericardial effusions was noted. The DCMRL portion of the examination was also evaluated for abnormal lymphatic flow in the upper chest and neck, axilla, perihilar region, lungs, pleural space, periportal distribution, mesentery, body wall, and dermal backflow into the lower abdomen and upper thigh. Presence or absence of the thoracic duct was noted.

A chart review was performed and clinical histories were recorded. The number of hospital days and days in the intensive care unit, on a ventilator, and on extracorporeal membrane oxygenation were recorded up to 120 days of life. Mortality was also recorded even after 120 days.

RESULTS

Patient Population

A total of five patients met the inclusion criteria, one of whom was prenatally diagnosed with hypoplastic left heart syndrome (HLHS) with a 5-mm-high atrial septal defect. Pertinent prenatal and postnatal imaging findings are listed in Table 1.

Prenatal Findings

"Nutmeg lung" was present in all five patients on evaluation of fetal MRI and in four patients on evaluation of the fetal US studies (Fig 1a). Prenatally, all five patients had pleural effusions. One patient (patient 2; Tables 1 and 2) had body wall edema prenatally. The patient with HLHS (patient 5; Tables 1 and 2) was the only one who had ascites prenatally.

Postnatal Imaging

3D T2 SPACE

Postnatal MRI with 3D T2 SPACE revealed increased signal in the upper chest and neck in four of five patients and increased signal within the retroperitoneum and mediastinum in all five patients. Branching increased interstitial high signal within the lung parenchyma (similar to the nutmeg lung appearance described prenatally) and trace ascites was seen in all five patients. Periportal edema was present in four of five patients.

Contrast Lymphangiography

DCMRL demonstrated lymphatic flow to the pleural space in four of five patients (Fig 1c), and was absent in the patient diagnosed with HLHS (patient 5; Tables 1 and 2). Lymphatic flow to the abdominal cavity was not seen in any of the five patients. Dermal backflow was seen in one of five patients (patient 2; Tables 1 and 2). There was increased enhancement of the retroperitoneum in all five patients. The thoracic duct was not visualized on DCMRL in two of five

TABLE 1. Presence or Absence of Prenatal and Postnatal Imaging Findings of the Five Patients with Neonatal Lymphatic Flow Disorder

		Nutmeg Lung on Fetal US	Nutmeg Lung on Fetal MRI	Prenatal		Postnatal 3D T2 SPACE				Postnatal DCMRL Abdominal Cavity		
Patients	Final Dx	(Y/N)	(Y/N)	Ascites	Body Wall Edema	Neck/ Supraclavicular (Y/N)	Mediastinum/ Perihilar (Y/N)	Lung Interstitium (Y/N)	Periportal (Y/N)	RP (Y/N)	Pleural Space (Y/N)	Dermal Backflow (Y/N)	Thoracic Duct Seen (Y/N)
1	NC	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y
2	CLFD	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N
3	NC	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	N
4	NC	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y
5	HLHS	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y

3D, three dimensional; CLFD, central lymphatic flow disorder; DCMRL, dynamic contrast-enhanced magnetic resonance lymphangiography; Dx, diagnosis; HLHS, hypoplastic left heart syndrome; MRI, magnetic resonance imaging; N, no; NC, neonatal chylothorax; RP, retroperitoneum; US, ultrasound; Y, yes.

patients, was dilated in two patients, and was small in a single patient.

Conventional lymphangiography was performed in three patients, all of whom had collateral lymphatic flow to the lung. After analyzing the results of the DCMRL and CL, the three patients (patients 1, 3, and 4; Tables 1 and 2) that demonstrated dynamic lymphatic flow to the lungs without flow to additional compartments and were classified as neonatal chylothorax (NC). One patient (patient 2; Tables 1 and 2) who demonstrated dermal backflow, in addition to dynamic perfusion to the lungs, was diagnosed with central lymphatic flow disorder (CLFD) (Fig 2) (9). The last patient (patient 5; Tables 1 and 2) who did not have dynamic perfusion to the lungs or additional compartments maintained a diagnosis of HLHS.

Outcome

Table 2 lists the treatment and outcomes of the patients, including the number of hospital days, ventilator days, intensive care unit days, and extracorporeal membrane oxygenation days during the first 120 days of life.

Mean hospital duration in the first 4 months of life was 51 days (range 5–113) in the three patients diagnosed with NC (patients 1, 3, and 4; Tables 1 and 2). The hospital duration in the first 4 months of life was 75 days in the patient diagnosed with CLFD and 120 days in the patient with HLHS. The patient diagnosed with CLFD (patient 2; Tables 1 and 2) and HLHS (patient 5; Tables 1 and 2) expired after 120 days of age because of respiratory distress.

Lymphatic intervention using an oil-based contrast agent (Lipiodol, Guerbet, Bloomington, IN) was performed in two patients (patients 1 and 4; Tables 1 and 2), both were classified as NC. The pleural effusions in the two treated patients with NC resolved postembolization treatment with injection of the Lipiodol as described by Gray et al. (3). The pleural effusion in the last patient diagnosed with NC resolved with conservative therapy.

DISCUSSION

The lymphatic system plays an essential role in both circulatory and organ perfusion homeostasis (15). In this retrospective case series, we describe both the prenatal and the postnatal appearance of the lymphatic system evaluated with DCMRL. Understanding these disorders poses a challenge as the nomenclature of these lymphatic anomalies is often confusing and inconsistent (15,16). Pulmonary lymphangiectasia has been described as dilatation of the pulmonary lymphatics, which may be congenital or acquired (17,18). The incidence of pulmonary lymphangiectasia is unknown, with autopsy studies demonstrating 0.5%–1% of stillborn or neonatal deaths of patients presenting prenatally with non–immune fetal hydrops and NC (18). Mortality rates of pulmonary lymphangiectasia are reportedly high, being between 50% and 98% (18). In patients with NC, abnormal pulmonary lymphatic perfusion constitutes the only lymphatic flow abnormality. This is in contrast to patients who have CLFD, where abnormal

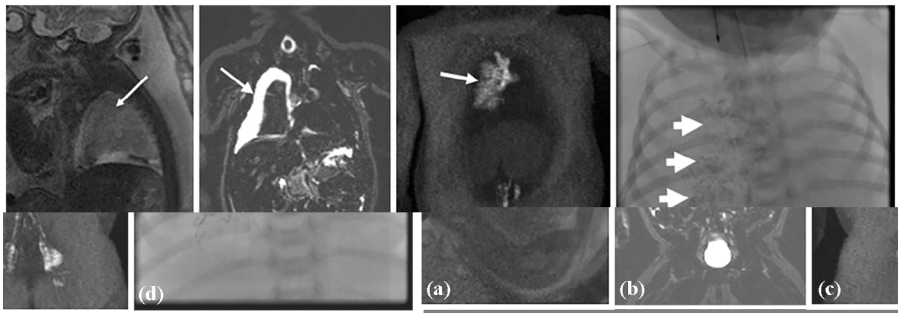

Figure 1. Neonatal chylothorax. **(a)** Sagittal T2 single shot FSE image of a 24-week fetus demonstrating tubular high signal structures in the lungs *(arrow)*, characteristic of "nutmeg lung" along with a right pleural effusion. **(b)** Coronal T2-weighted image at 20 days of life demonstrates a right pleural effusion *(arrow)*. **(c)** Maximum intensity projection (MIP) from a dynamic contrast-enhanced MR lymphangiogram at 20 days of life shows lymphatic perfusion of the right lung *(arrow)* corresponding to the area of pleural effusion. **(d)** Conventional lymphangiography at 20 days of life demonstrates the flow of oil-based contrast into the pathologic lymphatic channels of the right lung *(white arrows)*.

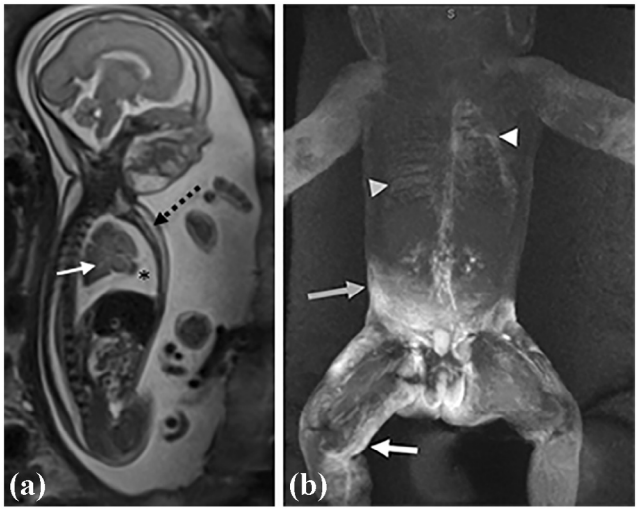

Figure 2. Central lymphatic flow disorder. **(a)** Sagittal T2 single shot FSE image of a 27-week fetus demonstrating subtle branching T2 signal with an overall increase in signal intensity of the lung parenchyma *(arrow)* due to retained fluid in lymphatic channels, consistent with "nutmeg lung" with a pleural effusion (*) and skin thickening *(dotted arrow)*. **(b)** Maximum intensity projection (MIP) from a dynamic contrast-enhanced MR lymphangiogram at 64 days of age demonstrating significant dermal backflow into the legs *(white arrow)*, genitals, left lung *(white arrowhead)*, intercostals *(gray arrowhead)*, and abdominal wall *(gray arrow)*.

pulmonary lymphatic perfusion is just one of the flow abnormalities present, implying a more global lymphatic dysfunction. Although pulmonary lymphangiectasia has been previously described in the literature, differentiating the underlying cause, as NC or CLFD, is important given there may be different prognostic outcomes.

The International Society for the Study of Vascular Anomalies classifies lymphatic malformations into five categories: common lymphatic malformations, generalized lymphatic anomaly, lymphatic malformation in Gorham-Stout disease, channel type lymphatic malformation, and primary lymphedema (16). Common lymphatic malformations comprised macrocystic, microcystic, and mixed cystic lymphatic malformations. Generalized lymphatic anomaly is characterized by visceral involvement, osteolysis, or central conducting lymphatic anomalies, whereas Gorham-Stout disease involves osteolysis with cortical disruption (16). Channel-type lymphatic malformations are due to a defect in the process for the evacuation of chyle, either from obstruction or aplasia (16). If categorized by the International Society for the Study of Vascular Anomalies classification, our series of patients would be classified as channel-type lymphatic malformations as there is disruption of the lymphatic flow or evacuation of chyle.

In our series of patients, there was only a single patient who met the criteria for CLFD given the dermal backflow present on the DCMRL. All patients prenatally demonstrated "nutmeg" lung but only one of these patients had underlying congenital heart disease. Given the prior series of the correlation of HLHS with "nutmeg" lung (13), the presence of additional patients without congenital heart disease raises the possibility of a primary underlying lymphatic disorder rather than just a secondary etiology. In our series, the single patient with HLHS differed from the patients without congenital heart disease in that there was no abnormal lymphatic perfusion to the lungs on the DCMRL despite comparable findings on conventional T2-weighted imaging.

It has been previously reported that HLHS patients with "nutmeg" lung have higher mortality or need of transplant (13). Additionally, the same authors reported a higher incidence of restrictive or intact atrial septum with "nutmeg lung" (13). Our single patient with HLHS and "nutmeg lung" did not have a restrictive atrial septum but did have abnormal findings on T2-weighted imaging with eventual demise following refractory hypoxia after bidirectional Glenn. This patient did not have final surgical correction with Fontan palliation.

As opposed to the patients diagnosed with NC and HLHS, the patient with CLFD demonstrated body wall edema on prenatal imaging and ultimately expired because of refractory chylous effusions. Postnatal findings of dermal backflow on DCMRL may correlate with prenatal body wall edema and may be an ominous sign, possibly due to more severe impedance to normal central lymphatic flow. The three patients diagnosed with NC only had abnormal lymphatic

TABLE 2. Lymphatic Intervention Performed Along with Outcomes of Five Patients with Neonatal Lymphatic Disorders

Patients	Dx	Lymphatic Intervention	Number of Days During the First 120 Days of Life				Final Outcome
			Hospital	ICU	Ventilator	ECMO	
1	NC	Lipiodol injection	113	71	111	0	Stable small pleural effusion without reaccumulation
2	CLFD	None	75	75	66	0	Continued chylous effusions until demise due to respiratory distress
3	NC	None	5	5	0	0	Resolution of pleural fluid without reaccumulation
4	NC	Lipiodol injection	34	34	0	0	Improvement of pleural effusion without reaccumulation
5	HLHS	None	120	120	120	5	Improving pleural effusion with refractory hypoxia post-Glenn with eventual demise

CLFD, central lymphatic flow disorder; Dx, diagnosis; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; ICU, intensive care unit; NC, neonatal chylothorax.

perfusion to the lungs and pleural space postnatally, demonstrated no abdominal ascites or body wall edema prenatally, and had improved pleural effusions and improved survival compared to the patient with CLFD.

The main limitation of this study is the small number of patients and the retrospective nature. In this retrospective review, all imaging examinations and procedures were performed based on clinical need. Additionally, although two of five patients expired, there was only short-term follow-up in the surviving patients. Long-term follow-up is needed to better understand the outcome of patients with NC.

In conclusion, NLDs can be recognized on prenatal and postnatal imaging and may be primary, as in NC or CLFD, or secondary as seen in patient with HLHS. In this small series, nutmeg lung was present in all patients and may be easier to recognize with fetal MRI than US. Prenatal imaging demonstrates that body wall edema may correlate with postnatal dermal backflow, a finding that may carry a poor prognosis in the patient diagnosed with CLFD. Prenatal imaging may guide further postnatal imaging with DCMRL along with treatment and interventions in patients with NLD.

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